



## King's Research Portal

DOI:

[10.1016/j.jid.2017.07.848](https://doi.org/10.1016/j.jid.2017.07.848)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Jabbar-Lopez, Z. K., Yiu, Z. Z. N., Ward, V., Exton, L. S., Mohd Mustapa, M. F., Samarasekera, E., Burden, A. D., Murphy, R., Owen, C. M., Parslew, R., Venning, V., Warren, R. B., & Smith, C. H. (2017). Author Reply to: Letter to the Editor in Response to recently published article, 'Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis'. *Journal of Investigative Dermatology*, 137(12), 2644-2646. <https://doi.org/10.1016/j.jid.2017.07.848>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# Accepted Manuscript

Author Reply to: Letter to the Editor in Response to recently published article, 'Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis'

Zarif K. Jabbar-Lopez, Zenas Z.N. Yiu, Victoria Ward, Lesley S. Exton, M Firouz Mohd Mustapa, Eleanor Samarasekera, A David Burden, Ruth Murphy, Caroline M. Owen, Richard Parslew, Vanessa Venning, Richard B. Warren, Catherine H. Smith

PII: S0022-202X(17)32833-6

DOI: [10.1016/j.jid.2017.07.848](https://doi.org/10.1016/j.jid.2017.07.848)

Reference: JID 1041

To appear in: *The Journal of Investigative Dermatology*

Received Date: 14 July 2017

Accepted Date: 23 July 2017

Please cite this article as: Jabbar-Lopez ZK, Yiu ZZN, Ward V, Exton LS, Mohd Mustapa MF, Samarasekera E, Burden AD, Murphy R, Owen CM, Parslew R, Venning V, Warren RB, Smith CH, Author Reply to: Letter to the Editor in Response to recently published article, 'Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis', *The Journal of Investigative Dermatology* (2017), doi: 10.1016/j.jid.2017.07.848.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



Author Reply to: Letter to the Editor in Response to recently published article, '**Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis**'

Zarif K Jabbar-Lopez<sup>1</sup>, Zenas Z N Yiu<sup>2</sup>, Victoria Ward<sup>3</sup>, Lesley S Exton<sup>4</sup>, M Firouz Mohd Mustapa<sup>4</sup>, Eleanor Samarasekera<sup>5</sup>, A David Burden<sup>6</sup>, Ruth Murphy<sup>7</sup>, Caroline M. Owen<sup>8</sup>, Richard Parslew<sup>9</sup>, Vanessa Venning<sup>10</sup>, Richard B Warren<sup>2</sup>, Catherine H Smith<sup>1</sup>

<sup>1</sup>St John's Institute of Dermatology, Guy's and St Thomas' NHS Foundation Trust & King's College London, UK

<sup>2</sup>Dermatology Centre, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

<sup>3</sup>University College London Hospital, London, UK

<sup>4</sup>British Association of Dermatologists, London, UK

<sup>5</sup>National Guideline Centre, Royal College of Physicians, London, UK

<sup>6</sup>Department of Dermatology, Royal Infirmary of Edinburgh, Edinburgh, UK

<sup>7</sup>Sheffield University Teaching Hospitals and Sheffield Children's Hospitals, Sheffield, UK

<sup>8</sup>Department of Dermatology, East Lancashire Hospitals NHS Trust, Royal Blackburn Hospital, Blackburn, UK

<sup>9</sup>Department of Dermatology, Royal Liverpool and Broadgreen University Hospitals Trust. Liverpool, UK

<sup>10</sup>Department of Dermatology, Oxford University Hospitals Foundation Trust, Oxford, UK

#### Word Count

995/1000

#### Corresponding Author

Prof. Catherine H. Smith, MD, FRCP  
St John's Institute of Dermatology,  
9<sup>th</sup> Floor, Tower Wing, Guy's Hospital,  
Great Maze Pond, London SE1 9RT, UK.  
E-mail: [catherine.smith@kcl.ac.uk](mailto:catherine.smith@kcl.ac.uk)

#### Conflicts of Interest

ADB consults and lectures for Abbvie, Amgen, Eli Lilly, Novartis, Pfizer, Celgene, Janssen, and Boehringer Ingelheim. CHS has received departmental research funding from Abbvie, Pfizer, Novartis, GSK, Roche, Regeneron, and Janssen. RBW has acted as a consultant and/or speaker and/or received research grants for Abbvie, Amgen, Almirall, Celgene, Boehringer, Eli Lilly, Pfizer, Leo, Novartis, Xenoport, and Janssen. CMO, ES, LSE, MFMM, RP, VV, ZKJ-L, and ZZNY have no conflicts of interest to declare.

#### Abbreviations

AE – Adverse Event; CI – Confidence Interval; NICE – National Institute for Health and Care Excellence; NMA – Network meta-analysis; PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SUCRA – Surface Under the Cumulative Ranking Curve

Dear Editor,

We thank Professor Reich and colleagues for their correspondence on our paper (Jabbar-Lopez et al., 2017). They helpfully highlight the IXORA-S trial comparing ixekizumab with ustekinumab for moderate-severe plaque psoriasis (Reich et al., 2017). This was published after our search cut-off date and so was not included in our review.

Reich et al. state that direct comparisons within a clinical trial provide the best evidence for evaluation of a drug. We agree that when a large (well-powered), high quality RCT has been performed the inclusion of indirect evidence adds little. However, IXORA-S was a trial of 302 participants and therefore underpowered to detect meaningful differences between treatments for less common outcomes, such as those related to safety. RCTs are not usually powered to show differences in adverse events (AEs) and so meta-analysis can be useful; by pooling data, power may be increased (Higgins JPT, 2011).

Our NMA correctly estimated the efficacy of ixekizumab compared to ustekinumab at 12 weeks (NMA: OR 3.09, 95% CI 1.89, 5.06 compared to IXORA-S OR 3.67, 95% CI 2.25, 5.97) (Reich et al., 2017). This suggests that the analytical approach taken in our NMA is functioning correctly. We know that the efficacy results from IXORA-S are likely to be correct as the study was powered to detect such a difference. We can be less certain whether the IXORA-S estimates for withdrawal due to AEs are true (i.e. that there is no difference between withdrawal due to AE between ixekizumab and ustekinumab) or the result of type II error. Furthermore, Reich et al. have chosen to compare the results of our 12-16 week NMA to the 24-week results from IXORA-S. This time point was outside the scope of our NMA and not comparable to 12-16 week data. Considering just the 12-week data reported in Reich et al. 2017, the number of withdrawals due to AE was 0 (ustekinumab) and 2 (ixekizumab). On the risk difference scale this equates to a 1% higher absolute risk of withdrawal due to AE (95% CI -1%, 4%) with ixekizumab versus ustekinumab, which is consistent with our NMA estimate of 2.5% (95% CI 0.6%, 6.3%), Table 1. Again, this suggests that the methodology is working. We state in our discussion that "The withdrawal due to adverse event results may be less reliable due

to the low number of events...” Furthermore, we highlight the low absolute numbers of events “(generally between 1 and 2%), reflected in the wide CI of the estimates”.

We agree that considering any relative performance measure, whether pairwise odds ratios or ranking measures such as surface under the cumulative ranking curve (SUCRA), or probability of being best, in isolation, can be misleading. Hence, our efforts to provide both relative and absolute estimates for the outcomes. Two thirds of published NMAs include rankings (Bafeta et al., 2014) and expert groups such as the International Society for Pharmacoeconomics and Outcomes Research Task Force recommend ranking as a way of presenting NMA results (Jansen et al., 2011). The SUCRA accounts for the location and the variance of all relative treatment effects (Salanti et al., 2011) and as such the PRISMA-NMA statement and checklist (Item 13) encourage use of SUCRAs as a robust measure of ranking (Hutton et al., 2015). This approach has been widely used in other NMAs, including for psoriasis (Gomez-Garcia et al., 2017), and Cochrane reviews in other fields, for example (Westby et al., 2017). Indeed, rankings have been used in an NMA focused solely on ixekizumab's efficacy (Hartz et al., 2016) and this information was included in the single technology appraisal submission to the UK National Institute for Health and Care Excellence (2016).

We chose withdrawal due to AEs as a proxy for tolerability following expert consensus. We agree that reasons for withdrawal due to AEs are important, however, these data were not consistently available from published studies. We thank Reich et al. for highlighting other (rare) safety outcomes (e.g. serious infections) and agree these data need to be considered when making treatment decisions, as discussed in our recent update to the British Association of Dermatologists guidelines for biologic therapy for psoriasis (Smith et al., 2017). However, these arguments do not mean the conclusions we made based on our NMA are incorrect (or that the methodology is flawed).

In our discussion, and consistent with Figure 1 (Reich), we highlight that the differences in withdrawal due to AEs between the interventions were small in absolute terms e.g. 2.5% with ixekizumab compared to ustekinumab. While Figure 1 (Reich) accurately represents the data from our Table 1, it is not particularly helpful for clinicians or patients as +/- 50% risk difference of withdrawals due to adverse events would not be expected for approved treatments. We have re-plotted the graph with a

more clinically meaningful range of +/- 15% along with error bars from 95% confidence intervals, as even an absolute difference in risk of a few percent may be important for some patients. (Figure 1)

We agree that the influence of dose on outcomes is important to consider and Reich et al. highlight the improvement in ixekizumab relative ranking from 7<sup>th</sup> to 6<sup>th</sup> in terms of tolerability when the analysis was restricted to licensed doses. Consistent with the approach taken in the cited recent pooled safety analysis of ixekizumab, we also considered it appropriate to include data from trials of non-label doses (Strober et al., 2017). As discussed, the differences may be true differences due to different doses, or may reflect the reduced precision seen in the smaller network of studies looking only at licensed doses, particularly for this less frequent outcome. Accordingly, we concluded that 'data on tolerability should be interpreted cautiously'.

In summary, our data analysis concurs with Reich's and colleagues' conclusion that 'ixekizumab has a very high efficacy and is well tolerated' (based on the absolute number of withdrawals due to AEs). However, we also consider the conclusions we made about the relative efficacy and tolerability of the different interventions, to be correct.

## References

- Single Technology Appraisal: Ixekizumab for treating moderate to severe plaque psoriasis [ID904] National Institute for Health and Care Excellence. Online: <https://www.nice.org.uk/guidance/ta442/documents/committee-papers-3>; NICE; 2016.
- Bafeta A, Trinquart L, Seror R, Ravaud P. Reporting of results from network meta-analyses: methodological systematic review. *BMJ* 2014;348:g1741.
- Gomez-Garcia F, Epstein D, Isla-Tejera B, Lorente A, Velez Garcia-Nieto A, Ruano J. Short-term efficacy and safety of new biological agents targeting the interleukin-23-T helper 17 pathway for moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis. *Br J Dermatol* 2017;176(3):594-603.
- Hartz S, Walzer S, Dutronc Y, Kiri SH, Schacht A, Dakin H. Network Meta-Analysis to Evaluate the Efficacy of Ixekizumab in the Treatment of Moderate-to-Severe Psoriasis. *Value Health* 2016;19(7):A576-A.
- Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2011.
- Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med* 2015;162(11):777-84.
- Jabbar-Lopez ZK, Yiu ZZN, Ward V, Exton LS, Mohd Mustapa MF, Samarasekera E, et al. Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis. *J Invest Dermatol* 2017.
- Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011;14(4):417-28.
- Reich K, Pinter A, Lacour JP, Ferrandiz C, Micali G, French LE, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a Phase 3 study. *Br J Dermatol* 2017.
- Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *Journal of Clinical Epidemiology* 2011;64(2):163-71.
- Smith CH, Jabbar-Lopez ZK, Yiu ZZ, Bale T, Burden AD, Coates LC, et al. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *Br J Dermatol* 2017.
- Strober B, Leonardi C, Papp KA, Mrowietz U, Ohtsuki M, Bissonnette R, et al. Short- and long-term safety outcomes with ixekizumab from 7 clinical trials in psoriasis: Etanercept comparisons and integrated data. *Journal of the American Academy of Dermatology* 2017;76(3):432-+.
- Westby MJ, Dumville JC, Soares MO, Stubbs N, Norman G. Dressings and topical agents for treating pressure ulcers. *Cochrane Database Syst Rev* 2017;6:CD011947.

**Figure 1: Efficacy compared to tolerability at Weeks 12 to 16 based on Figure 1 from Letter to the Editor by Reich et al\***

\*Risk differences from Table 1 of Jabbar-Lopez et al.

Abbreviations: ADA – adalimumab; ETA – etanercept; INF – infliximab; IXE – ixekizumab; MTX – methotrexate; PBO – placebo; SEC – secukinumab; UST – ustekinumab



